III. REMARKS

Claim Status

The examiner acknowledges applicant's election without traverse of Group I. Claims 1-5, 9-12 are prosecuted to the extent they read on the elected species. Claims 6-8, 13-39 are withdrawn from consideration as directed to non-elected species. Claims 40-43 are new.

Claim Rejections - 35 USC § 112

Claims 2 and 3 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that the claims list preferred species.

The claims have been amended to move the preferred species to new dependent claims to obviate this ground for rejection

Claim Rejections - 35 USC § 103(a)

Claims 1-5, 9-12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Dyrsting et al. (US 6,077,822) in view of Rayburn (WO 00112067) and Buschmann et al. EP 0 693 475 (equiv. to US 6,344,558).

As background before directly addressing the prior art, applicant notes that a large number of highly efficacious pharmaceutical active substances have a strongly bitter taste and often produce a sensation of nausea when administered orally to patients. In many patients this negative taste experience results in a lack of compliance with the dosage instructions as well as a less than satisfactory acceptance of the corresponding medicaments that already release such an active substance *on* ingestion (specification, page 1, 2nd paragraph).

The formulation of extremely water-soluble pharmaceutical active substances to form medicaments often presents problems in pharmaceutical practice. For example,

the production of medicaments with a controlled release is often complicated on account of the extremely good water solubility of salts of active substances. A delayed release of these active substances may for example be achieved by coating the medicament forms with delayed-release film coatings. This type of delayed release is however relatively complicated and expensive since delayed-release film coatings of aqueous coating systems for extremely water-soluble active constituents often constitute only an insufficient diffusion barrier. he production of these delayed-release active substance preparations therefore requires relatively complicated and expensive coating processes involving multilayer films. If such delayed-release coatings of organic solvents are applied, the associated environmental and solvent residue problems add to the costs of producing the corresponding preparations. (specification, page 1, paragraph 3).

The object of the present invention was to solve the problem of the lack of palatability of pharmaceutical compounds of active substances that have a bitter taste. A second problem addressed by the present invention is to simplify to formulation of pharmaceutical compounds of active substances that have a bitter taste. A third problem addressed by the present invention is the low effectiveness the delayed release profiles of current formulations of pharmaceutical compounds of active substances that have a bitter taste.

These problem s are solved according to the presently claimed invention by the provision of pharmaceutical, i.e. physiologically compatible, salts of a pharmaceutical active substance of formula I and at least one sugar substitute.

Applicant's claims stand rejected over a combination of references.

Dyrsting et al. relates to salts of biologically active organic molecules with sugar acids, in particular to substantially water-insoluble salts of a mono to octa-saccharide sugar acid having oxyacid groups with a biologically active organic compound selected from the group consisting of aminoglycosides, tetracyclines, polypetides and macrolides.

Rayburn, WO 00/12067, discloses that saccharinate salts of non-alkaloid organic bases provide improved organoleptic properties.

Buschmann et al. (the European equivalent of which was cited in the present application) describes 1-Phenyl-3-Dimethylaminopropane compounds such as (1 RS, 2RS)-3-(3-dimethylamino-1-hydroxy-1,2-dimethylpropylphenol and the general formation of salts. but is entirely silent about the formation of salts of these compounds with sugar substitutes such as saccharin, cyclamate or acesulfam.

Applicants traverse this ground for rejection.

Dyrsting et al. relates to different active pharmaceutical ingredients and to entirely different salt forming partners, namely to sugar acids instead of sugar substitutes.

Rayburn - which does not even mention analgesics - discloses an inconsistent trend with regard to the solubility of alkaloidal active substances (Rayburn, page 1, last paragraph). The saccharinate salt of vincamine, a pharmaceutically active alkaloid, was described as having improved solubility compared to conventional salts such as the hydrochloride. In contrast thereto, the saccharinate salt of Buspirone is reported to have reduced solubility compared to conventional salts, even though no experimental data is actually disclosed in said reference.

Even within one and the same group of active substances, such as the group of Alkaloid-saccharinates, there is non-uniform behavior with regard to solubility. As can be seen from the examples of the present application, in particular example 8, table 1, the specific alkaloid saccharinates mentioned therein such as morphine, codeine and the like, show a solubility that is reduced compared to their conventional salts such as their hydrochlorides or phosphates. This is particular surprising to the person skilled in the an, because the reference of Rayburn explicitly discloses that the saccharinate salts of alkaloidal compounds show improved solubility compared to their conventional salts (Rayburn, page 2, lines 6-8).

Buschmann et al. is entirely silent about the formation of salts of these compounds with sugar substitutes such as saccharin, cyclamate or acesulfam.

First, applicant notes that none of the cited references gives any hint suggesting the transfer of the pharmaceutically active compounds of general formula I into corresponding salts with sugar substitutes.

Furthermore, there is also no hint in the cited prior art to the inventive solution of the problems underlying the present invention.

As disclosed in the present application, it is surprisingly shown that the saccharinates of the alkaloidal compounds of present claim 1 show a reduced solubility compared to their conventional salts such as their hydrochlorides or phosphates (specification, example 8, table 1). This would not have been expected by the person skilled in the art in view of the cited references.

The formulation of the inventive pharmaceutical salts into medicaments, for example, the production of granules by extrusion, is also simplified. The pharmaceutical salts according to the invention furthermore permit, on account of their altered solubility, a more effective delayed release of the active substance using conventional delayed-release methods compared to normally used salts.

Delayed-release medicaments that contain pharmaceutical salts according to the invention may therefore be produced in a simpler and more cost-effective manner. The same is also true for other modifications of the medicaments according to the invention, such as for example medicaments with coatings resistant to gastric juices.

None of the cited references discloses or suggests that controlled release dosage forms on the basis of the inventively claimed salts may be prepared in a simple and efficient manner.

Thus, the cited references, read in combination, do not render the presently claimed invention obvious. Rather, it is only in knowledge of the presently claimed

invention that the Examiner is able to select and combine certain individual elements of the presently claimed invention. Such a hindsight approach, however, is inadmissible for judging the inventive step of a claimed invention.

Consequently, the presently claimed invention is not only novel, but also involves an inventive step over the cited prior art.

It is respectfully submitted that all of the claims present in the application are novel and patentable, and are in proper form for allowance. Accordingly, favorable consideration and allowance is respectfully requested. Should any unresolved issues remain, the Examiner is invited to call Applicants' attorney at the telephone number indicated below.

The Commissioner is hereby authorized to charge payment for the three month extension of time ($1020) and the four additional dependent claims ($200) as well as any other fees associated with this communication or credit any over payment to Deposit Account No. 16-1350.

Respectfully submitted,

30 July 2007

Geza C. Ziegler, Jr.
Reg. No. 44,004
Perman & Green, LLP
425 Post Road
Fairfield, CT 06824
(203) 259-1800
Customer No.: 2512

Date

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I hereby certify that this correspondence is being transmitted electronically, on the date indicated below, addressed to the Mail Stop AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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